VOLUME 26 · NUMBER 4 · FEBRUARY 1 2008

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Long-Term Results From a Randomized Phase II Trial of Standard- Versus Higher-Dose Imatinib Mesylate for Patients With Unresectable or Metastatic Gastrointestinal Stromal Tumors Expressing *KIT*

Charles D. Blanke, George D. Demetri, Margaret von Mehren, Michael C. Heinrich, Burton Eisenberg, Jonathan A. Fletcher, Christopher L. Corless, Christopher D.M. Fletcher, Peter J. Roberts, Daniela Heinz, Elisabeth Wehre, Zariana Nikolova, and Heikki Joensuu

From the Oregon Health and Science University Cancer Center and Portland Veterans Affairs Hospital, Portland, OR; Dana-Farber Cancer Institute, Boston, MA; Fox Chase Cancer Center, Philadelphia, PA; Dartmouth Hitchcock Medical Center, Lebanon, NH; Novartis Corp, Basel, Switzerland; University Hospital of Turku; and the Helsinki University Central Hospital, Helsinki Finland.

Submitted July 18, 2007; accepted September 7, 2007.

Supported by Grant No. ASOMO0014 from Novartis and from a Veterans' Affairs Merit Review.

C.D.B., G.D.D., M.v.M., and H.J. contributed equally to this work.

Presented at the ASCO Combined GI Symposium, January 19-21, 2007, Orlando, FL.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Corresponding author: Charles D. Blanke, MD, FACP, 3181 SouthWest Sam Jackson Park Rd, MC-L-586, Portland, OR 97239; e-mail: blankec@ohsu.edu.

0732-183X/08/2604-620/$20.00

DOI: 10.1200/JCO.2007.13.4403

ABSTRACT

Purpose
The outcome of patients diagnosed with advanced gastrointestinal stromal tumor (GIST) and treated long-term with imatinib mesylate is unknown. A previous report of a randomized phase II trial of imatinib mesylate in patients with incurable GIST detailed high response rates at both the 400 and the 600 mg/d dose levels. We conducted a long-term analysis of patients treated on the trial, including patients followed during an extension phase, to evaluate survival, patterns of failure, and potential prognostic factors, including tumor mutational status.

Patients and Methods
Patients with advanced GIST were enrolled onto an open-label, multicenter trial and were randomly assigned (1:1) to receive imatinib 400 versus 600 mg/d. Data were prospectively collected on *KIT* mutational status, total tumor area, and other potential prognostic factors. Patients were followed for a median of 63 months.

Results
One hundred forty-seven patients were enrolled: 73 were in arm A (imatinib 400 mg/d), and 74 were in arm B (imatinib 600 mg/d). Response rates, median progression-free survival, and median overall survival were essentially identical on both arms, and median survival was 57 months for all patients. Forty-one patients overall (28%) remained on the drug long-term. Female sex, the presence of an exon 11 mutation, and normal albumin and neutrophil levels were independently associated with better survival.

Conclusion
Nearly 50% of patients with advanced GIST who were treated with imatinib mesylate survived for more than 5 years, regardless of a 400 or 600 mg/d starting dose.

J Clin Oncol 26:620-625. © 2008 by American Society of Clinical Oncology

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract; they occur with an annual frequency of 10 to 14.5 per one million of the population.[1,2] No effective systemic treatments existed for GISTs before the availability of molecularly targeted kinase inhibitors.[3] However, the association between constitutively activated KIT (and later PDGFRA) signaling and GIST oncogenesis provided justification for testing a small molecule tyrosine kinase inhibitor in this tumor type.[4]

Imatinib mesylate is an oral, selective, small-molecule competitive inhibitor of KIT, PDGFRA, and other tyrosine kinases.[5-8] Based on preclinical studies and proven single-patient benefit, we conducted a phase II clinical trial to evaluate the efficacy and safety of imatinib in patients with advanced GIST.[8-10] This trial was originally designed as a 36-month core study, but a 4-year extension was added when a significant fraction of patients appeared to benefit from drug therapy and responses appeared durable. Objectives of the core study were to assess the initial clinical activity, safety, tolerability, and pharmacokinetics of imatinib while simultaneously assessing the frequency of *KIT* and *PDGFR* gene mutations and their relationship to long-term outcome. The extension study assessed long-term efficacy of the drug and also evaluated

the potential relationships between other putative prognostic factors and outcome.

One hundred forty-seven patients with advanced GIST were enrolled onto the core study and were randomly assigned to receive initial treatment with imatinib 400 or 600 mg/d. Based on a 9-month median follow-up period, the initial objective response rate for all patients was reported as 54%; 28% achieved stable disease, and 14% experienced disease progression within the first 6 months of treatment.[11] At the time of the initial report, neither the median duration of response nor the median overall survival had been reached,[11] and the long-term outcome of patients with advanced GIST who received imatinib mesylate was not yet known. Herein, we report the results from the 4-year extension study.

PATIENTS AND METHODS

Patients and Study Design

The core study, denoted study B2222, was a phase II, prospective, open-label, multicenter, randomized trial conducted at three study centers in the United States and at one in Finland. Adult patients with histologically confirmed, unresectable or metastatic GIST that expressed the CD117 antigen (as a marker of the KIT receptor) and with measurable disease based on Southwestern Oncology Group (SWOG) criteria[12] were eligible. Other eligibility criteria included an Eastern Cooperative Oncology Group performance score of 2 or less (later modified to ≤ 3); an estimated life expectancy of at least 6 months; and adequate hematologic, renal, and hepatic function. Informed consent was obtained from all patients, and appropriate institutional review board approval was garnered at each center.

Dosage and Administration of Imatinib

Patients were randomly assigned in a 1:1 ratio to receive initial doses of imatinib 400 or 600 mg/d. Patients with progressive disease on 400 mg/d, but otherwise in good clinical condition, could increase the imatinib dose to 600 mg/d. A protocol amendment later allowed dose escalation from 600 mg/d to 400 mg every 12 hours if the investigator believed this would clinically benefit the patient. Patients who completed the core study could enter a longer-term extension trial (which would provide an additional 4 years of imatinib) if they continued to demonstrate clinical benefit and if there were no significant safety issues. This extension study restricted entry to patients who had completed participation in the core trial.

Efficacy and Safety Evaluations

The primary efficacy parameter of the core study was best overall tumor response based on SWOG criteria.[12] Methods and timing of response assessment were previously published.[11] Secondary efficacy parameters analyzed for the extension study included duration of response, time to response, and overall survival.

Safety and tolerability assessments were performed on all patients who received at least one dose of imatinib. Adverse event severity was graded according to the National Cancer Institute Common Toxicity Criteria, version 2.0[13] but used a slightly stricter definition of grade 0 or 1 leukopenia and neutropenia. During the extension study, toxicity information was gathered only for serious adverse events.

Additional Evaluations

Tumor biopsy specimens were obtained from selected patients before and, whenever possible, after imatinib treatment for the histopathologic assessment of treatment and mutational analysis of the *KIT* and *PDGFRA* genes. Information on total tumor target lesion area and other potential prognostic factors was prospectively collected.

Statistical Analyses

Efficacy analyses were based on all randomly assigned patients who received at least one dose of imatinib. Response rates were calculated with a two-sided 95% confidence interval (Pearson-Clopper limits). Time-to-event analyses were performed using Kaplan-Meier methods.

The following potential prognostic variables were investigated for their impact on long-term outcomes: age (<65 *v* ≥ 65 years), sex, initial dose (400 *v* 600 mg/d), Eastern Cooperative Oncology Group performance status (score 0 *v* 1 *v* ≥ 2), primary site of tumor (stomach *v* other), sum area of tumor target lesions (<39.1 *v* ≥ 39.1 cm^2), time since diagnosis (<12, 12 to <24, or ≥ 24 months), prior chemotherapy, prior radiotherapy, liver or lung involvement, mutational status of exon 11 (no *v* yes), and categories of the following baseline laboratory values: neutrophils, platelets, hemoglobin, albumin, and granulocytes. For the prognostic factors evaluation, each potential candidate was initially assessed by univariate analysis. Factors found significant at $P < .1$ were included in a multivariate Cox regression model. Thereafter, a stepwise selection procedure was applied to select the most relevant prognostic factors. Only factors that remained significant at the .05 level during the selection procedure were included in the final model. The appropriateness of the proportional hazards assumption was checked. Factors which deviated substantially from the assumption were identified either in the log-log survival curve plots visually or by a significant deviation of the assumption of constant hazard over time in the Cox model. $P < .05$ was used to indicate a nonconstant hazard over time. The multivariate analysis included patients for whom there were data for all modeled variables.

Data cutoff for this analysis was May 26, 2006. Median follow-up at that time was 63 months (maximum, 71 months).

RESULTS

Patient Characteristics and Disposition

In total, 147 patients were enrolled onto the core study between July 2000 and June 2001. Sixty-seven (46%) completed the core portion and 56 (38% of the total initial population) entered the extension study. There were no meaningful differences between the standard or higher-dose patients regarding percentage entering the extension study. Patients treated on the extension study had received imatinib for up to 5.9 years at the data cutoff date. Forty-six patients (31% of the original cohort) were still taking imatinib at 5 years, and forty-one patients (28%) were still being actively treated at the time of data cutoff.

Efficacy

During a follow-up of up to 71 months, two patients (1.4%) achieved complete responses and 98 patients (66.7%) demonstrated partial responses, providing an overall objective response rate of 68.1% (95% CI, 59.8% to 75.5%; Table 1). The overall response rates were similar between arms, though both complete responses came

Table 1. Best Response by Dose Group and for All Patients

Best Response	Imitimab Dose Group: 400 mg (n = 73) No.	%	600 mg (n = 74) No.	%	All Patients (N = 147) No.	%
Response						
Complete	0	0	2	2.7	2	1.4
Partial	50	68.5	48	64.9	98	66.7
95% CI	56.5 to 78.9		55.6 to 78.0		59.8 to 75.5	
Disease						
Stable	10	13.7	13	17.6	23	15.6
Progressive	11	15.1	6	8.1	17	11.6
Not assessable/unknown	2	2.7	5	6.8	7	4.8

from the higher-dose imatinib group. Twenty-three other patients (15.6%) had prolonged stable disease, the majority of these for greater than 1 year. Seventeen patients (11.6%) exhibited progression.

Median time to response in patients who achieved at least a confirmed partial response was 2.7 months. Of note, 25% of these patients took more than 5.3 months to achieve their response (Table 2). No significant difference in time to response was noted between the two dose groups ($P = .1039$).

The median duration of response was 29 months (95% CI, 22 to 43). The response duration did not differ between patients given imatinib 400 versus 600 mg/d ($P = .7785$).

The median time to progression was 24 months overall, 20 months in the 400 mg/d dose group, and 26 months in the 600 mg/d dose group ($P = .3712$, log-rank test; Fig 1). Sixty-seven of the 100 responding patients progressed and/or died. The median time to progression for responding patients was 33 months, whereas it was 12 months in patients with stable disease. The estimated proportion of patients without progression at 60 months was 34% for responding patients and 22% for patients with stable disease.

Seventy-seven (52%) of the 147 study patients have died, including 40 (55%) in the 400 mg/d dose group and 37 (50%) in the 600 mg/d dose group. The overwhelming majority (86% overall) died of GIST, whereas causes of death in the remaining eight patients included one each of the following: breast cancer, probable pulmonary embolism, myocardial infarction, cardiac arrest, respiratory failure, cerebrovascular accident, leukemia, and septicemia with shock. The cause was unknown in three patients. Estimated median overall survival was 57 months for the total population; no significant differences in survival were observed between the two dose groups (hazard ratio [HR] 0.873; $P = .5506$, log-rank test; Fig 2).

Overall survival was equivalent in patients who achieved either stable disease or a partial response, and both groups demonstrated substantially longer survival (estimated 5-year survival, 55%) than patients who initially progressed on imatinib (5-year survival, 9%; Fig 3).

After progression, 43 patients in arm A and 13 in arm B had imatinib dose increases. Seven patients (16%) from the 400 mg/d group achieved a confirmed partial response, and 4 (9%) achieved stable disease after dose escalation, which provided a tumor control rate of 26%. One patient (7%) achieved a partial response and one patient experienced stable disease in the 600 mg/d group, which provided a tumor control rate of 15%.

KIT and *PDGFRA* mutational analyses were performed for 128 (87%) of the 147 patients (testing mechanisms described previously[14]). The overall and specific frequencies of *KIT* and PDGFR mutations and the response rates by subgroups have not significantly changed from the original publication (Appendix Table A1, online only).[14] Estimated median survival was 63 months for patients with *KIT* exon 11 mutations and was 44 months for patients with *KIT* exon 9 mutations (Appendix Fig A1, online only). Significantly shorter median overall survival (26 months) was noted in patients with other *KIT* mutations and with no mutations (overall $P = .005$, log-rank test).

Table 2. Time to Response

Response (N = 100)	Time to Response (months)
Minimum	0.8
Maximum	39
Median*	2.7
75% achieving response	5.3

NOTE. Time to response measured in all patients (in 400 and 600 mg dose groups combined) who achieved an objective response.
*Median = 50% achieving response.

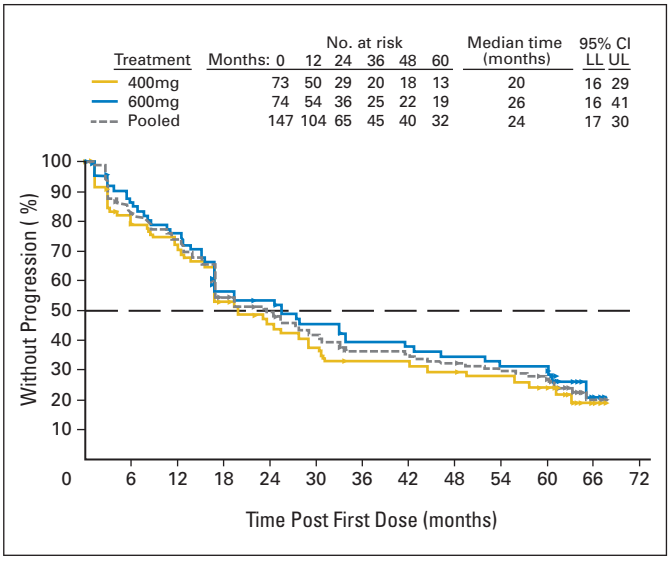

Fig 1. Time to progression. LL, lower limit; UL, upper limit.

Long-Term Safety and Tolerability of Imatinib Therapy for Advanced GIST

The safety of imatinib in our patient population was previously discussed.[11] Imatinib remained well tolerated over long-term administration, as no new serious adverse events emerged on this trial with the longer follow-up. Specifically, no patient withdrew from the extension study because of adverse events.

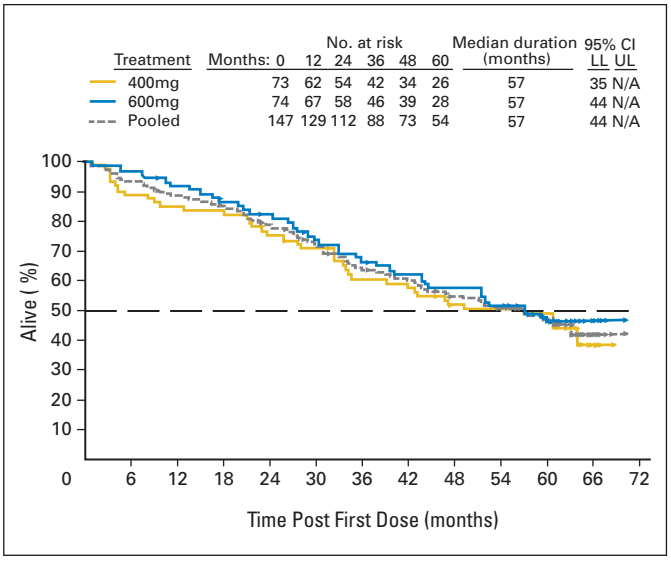

Fig 2. Overall survival. LL, lower limit; UL, upper limit; N/A, not available.

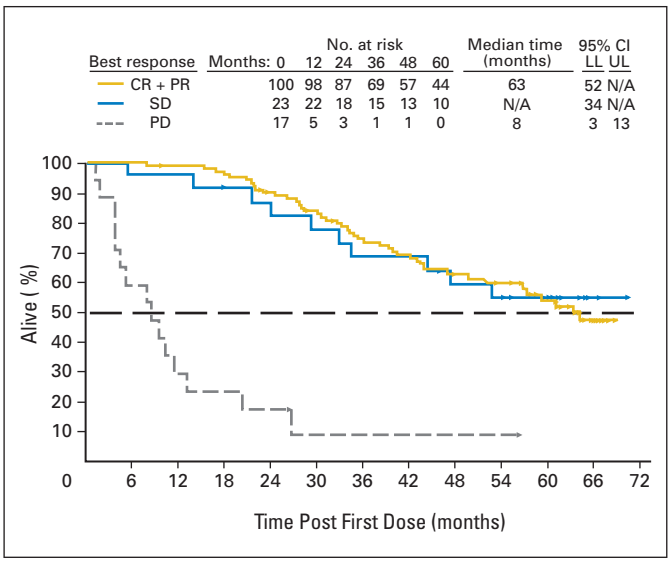

Fig 3. Overall survival according to best response. LL, lower limit; UL, upper limit; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; N/A, not available.

Prognostic Factors

Twenty-three patients were missing one or more pieces of data intended for the modeled multivariate analysis. Thus, 124 total patients were included in the multivariate analysis (Table 3). The following were associated with better prognosis: female sex, exon 11 mutation, normal albumin, and normal neutrophil levels. Because some factors deviated significantly from the assumption of proportional hazards, a piecewise Cox regression was performed that divided the time scale of overall survival time into two periods, from 0 to 30 months and from 30 to 72 months. In the first time period, patients with exon 11 mutations ($P < .0001$; HR, 0.148), normal albumin ($P = .0050$; HR, 0.369) and neutrophils less than 4.5×10^9/L ($P = .0055$; HR, 0.345) experienced significantly better survival. In the second time period, sex remained in the final model ($P = .0039$; HR, 0.304 for females compared with males), as did normal albumin ($P = .0114$; HR, 0.406). Exon 11 status did not remain in the final model in the second time period. Thus, the effect of exon 11 mutations on overall survival during the 6-year study period mainly resulted from their strong effect during the first 30 months, whereas the highly significant effect of sex resulted from its contribution after 30 months.

DISCUSSION

Imatinib mesylate, a semi-selective inhibitor of uncontrolled kinase activity of KIT and PDGFRA, can control advanced GIST in a large proportion of patients for more than 5 years. The long-term results of imatinib therapy reported here demonstrate objective responses that were maintained for greater than 2 years (median, 29 months) and that provided a median overall survival of 57 months. Twenty-eight percent of patients continue to take the drug on study after a follow-up of up to 71 months. These results are substantially superior to historical series, in which patients with advanced or metastatic GIST were treated with standard chemotherapy.

Several issues of interest emerged with the longer follow-up of patients on this trial. First, many objective responses evolved slowly. In 25% of the patients, an objective response was achieved only after 5.3 to 39 months of imatinib treatment. Interestingly, the original published report of this trial detailed an objective response rate of 54%, which was substantially lower than the 68% rate seen here.[11] This slow evolution of response probably explains the discrepancy. Additionally, response assessments were based on conventional criteria, which used changes in tumor size.[12] Response assessment systems using density and/or smaller changes in size are much more precise,[15] and it is likely they would yield information on potential responses more quickly. Similarly, this study report documents fewer absolute patient cases of progressive disease on each arm than did the original published manuscript.[11] As response criteria were identical for both assessments, this must be attributed to the difficulty in determining progression based on computed tomography– or magnetic resonance imaging–based size criteria alone. In fact, two of the three reclassified patients, formerly with progressive disease, are still on study without definite proof of disease progression. Next, long-term survival on imatinib was similar between GIST patients achieving an objective response by conventional criteria and those whose disease merely stabilized. Survival was equivalent despite a shorter time to progression in patients with stable disease compared with those who achieved a partial response on imatinib. This finding may imply that salvage therapy (potentially including increased imatinib doses, alternative tyrosine kinase inhibitors, or–rarely–surgery) is effective or possibly that continuing imatinib, even in the face of progression, delays death from GIST, as a substantial fraction of patients on study B2222 continued imatinib therapy after discontinuation from the study because of disease progression. The estimated median overall survival for patients who experienced disease progression within the first 6 months of study entry was quite short (36 weeks), which suggests that salvage therapy for this population is less effective and/or that the mechanisms of resistance to tyrosine kinase inhibition between this population and those with secondary imatinib resistance are quite different. Finally, no difference in outcome was seen between patients taking imatinib 400 or 600 mg/d. This result parallels the findings from two phase III studies that assessed imatinib 400 versus 800 mg/d.[16,17] Neither of those trials showed a progression-free survival advantage (the primary objective of each) for the initial higher dose.

Several patient and tumor characteristics were examined as potential prognostic factors. A phase III trial that examined imatinib 400 versus 800 mg/d in patients with advanced GIST suggested that low baseline hemoglobin and high baseline granulocyte levels predicted early resistance to imatinib mesylate, whereas large tumor size, high granulocyte count, nongastric primary tumor, and treatment with imatinib 400 mg/d were independently associated with late resistance.[17,18] On that trial, tumor bulk was represented by quantifying the single largest lesion. Our study showed that sex, performance status, mutational status, neutrophil count, and albumin level were independently associated with survival. Smaller tumor size and low performance score were prognostic in the univariate model but not in multivariate analysis. This trial differed in its assessment of tumor bulk by evaluation of the total area of all target lesions when utilizing the SWOG system. Patients with the bulkiest tumors had identical response rates compared with those who had the smallest tumor areas, but their survival appeared worse; however, this did not reach statistical significance when all other factors were included in the model, which possibly reflects factors such as tumor-related bleeding (Appendix Table A2; Appendix Figs A2 and A3, all online only). This is

Table 3. Prognostic Factors for Overall Survival Based On Univariate Analyses and Final Multivariate Model

Factor at Baseline	Univariate Analyses					Multivariate Analysis	
	Total No. of Patients	No. of Events	5-Year OS (%)	Hazard Ratio*	Log-Rank *P*	*P* (χ^2)	Hazard Ratio
Sex							
Male	83	53	38				
Female	64	24	61	0.506	.0048	.0093	0.487
ECOG PS							
0	62	27	57				
1	57	29	52				
≥ 2	28	21	17	1.696	.0003		
Exon 11 *v* other patients†							
No	42	29	30				
Yes	86	40	54	0.451	.0009	.0004	0.403
Size of tumor, cm^2							
< 39.1	36	12	68				
≥ 39.1	110	64	41	2.309	.0063		
Neutrophils, $\times 10^9$/L							
< 4.5	63	29	58				
≥ 4.5	81	48	38	1.837	.0092	.0023	2.249
Granulocytes, $\times 10^9$/L							
< 5	72	35	54				
≥ 5	72	42	39	1.654	.0271		
Hemoglobin, CTC grade							
0	70	30	56				
≥ 1	77	47	41	1.647	.0312		
Platelets, $\times 10^9$/L							
< 275	70	31	58				
≥ 275	77	46	38	1.662	.0276		
Albumin, CTC grade							
0	81	31	61				
≥ 1	66	46	32	2.295	.0002	.0007	2.347

Abbreviations: OS, overall survival; ECOG PS, Eastern Cooperative Oncology Group performance status; CTC, common toxicity criteria.
*In the category where no hazard ratio is given, it can be derived by taking the inverse of the hazard ratio in the other category.
†Excludes missing patients.

consistent with the hypothesis that a larger number of tumor cells should be quantitatively proportional to a greater likelihood of harboring more resistant clones. Nonetheless, one-third of patients with the bulkiest GISTs were long-term survivors.

On this trial, approximately one-fourth of patients whose imatinib dose was increased because of disease progression showed some clinical benefit. This finding is consistent with results from two large, phase III trials that compared imatinib 400 versus 800 mg/d in patients with incurable GIST.[19,20] On those trials, 88 and 133 patients, respectively, crossed over to the higher dose after progression; subsequently, 7% and 2.3%, respectively, responded; and 29% and 27.1%, respectively, exhibited stability. Thus, dose escalation of imatinib may be a reasonable initial step for patients with GIST who experienced disease progression on a lower dose of imatinib.

Longer follow-up of these patients confirms prior observations that kinase genotype is predictive of objective response and overall survival with imatinib use in GIST.[14] Patients with GIST who harbored *KIT* exon 11 mutations had a higher rate of objective response to imatinib (86%) than patients whose tumors harbored either a *KIT* exon 9 mutation (48%) or no detectable mutations in *KIT* or *PDGFRA* (0%), and they enjoyed superior event-free and overall survival rates as well. These findings are consistent with reported data from at least one other study that examined the relationship of *KIT* and *PDGFRA* mutations to response to imatinib, though that trial did detail a 23% response rate in patients who lack detectable mutations.[17,21] The phase III European Organisation for Research and Treatment of Cancer trial discussed above demonstrated that patients with exon 9 mutations have superior progression-free survival when initially treated with a higher dose of imatinib (800 *v* 400 mg/d)[17,21]; the number of patients with exon 9 mutations on our trial was too small to draw any conclusions.

This trial now reports the longest follow-up of any published study for patients with advanced GIST who were treated with imatinib mesylate. The results show that some patients achieved long-term and progression-free survival with drug therapy (> 5 years) and that imatinib mesylate is well tolerated during an administration period of years. Whether or not select patients with metastatic disease achieve normal life spans remains to be seen.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked

with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

Employment or Leadership Position: Daniela Heinz, Novartis (C); Elisabeth Wehre, Novartis (C); Zariana Nikolova, Novartis (C) **Consultant or Advisory Role:** George D. Demetri, Novartis (C), Pfizer (C), Infinity (C); Margaret von Mehren, Novartis (C); Michael C. Heinrich, Novartis (C), Molecular MD (C); Burton Eisenberg, Novartis (C); Christopher L. Corless, Novartis (C), Pfizer (C); Heikki Joensuu, Novartis (C) **Stock Ownership:** Michael C. Heinrich, Molecular MD; Daniela Heinz, Novartis; Elisabeth Wehre, Novartis; Zariana Nikolova, Novartis Honoraria: George D. Demetri, Novartis, Pfizer; Michael C. Heinrich, Novartis; Burton Eisenberg, Novartis; Christopher L. Corless, Novartis; Heikki Joensuu, Novartis **Research Funding:** Charles D. Blanke, Novartis; George D. Demetri, Novartis, Pfizer, Infinity; Margaret von Mehren, Novartis; Michael C. Heinrich, Novartis, Pfizer **Expert Testimony:** George D. Demetri, Novartis (U), Pfizer (U), Infinity (U)

AUTHOR CONTRIBUTIONS

Conception and design: Charles D. Blanke, George D. Demetri, Margaret von Mehren, Michael C. Heinrich, Burton Eisenberg, Peter J. Roberts, Heikki Joensuu
Financial support: George D. Demetri, Michael C. Heinrich
Administrative support: George D. Demetri, Margaret von Mehren
Provision of study materials or patients: Charles D. Blanke, George D. Demetri, Margaret von Mehren, Burton Eisenberg, Peter J. Roberts, Heikki Joensuu
Collection and assembly of data: Charles D. Blanke, George D. Demetri, Margaret von Mehren, Jonathan A. Fletcher, Christopher L. Corless, Daniela Heinz, Heikki Joensuu
Data analysis and interpretation: Charles D. Blanke, George D. Demetri, Margaret von Mehren, Michael C. Heinrich, Jonathan A. Fletcher, Christopher L. Corless, Christopher D.M. Fletcher, Daniela Heinz, Elisabeth Wehre, Zariana Nikolova, Heikki Joensuu
Manuscript writing: Charles D. Blanke, George D. Demetri, Margaret von Mehren, Elisabeth Wehre, Zariana Nikolova, Heikki Joensuu
Final approval of manuscript: Charles D. Blanke, George D. Demetri, Margaret von Mehren, Michael C. Heinrich, Jonathan A. Fletcher, Christopher D.M. Fletcher, Zariana Nikolova, Heikki Joensuu

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Appendix

The Appendix is included in the full-text version of this article, available online at www.jco.org. It is not included in the PDF version (via Adobe® Reader®).